Rh_o(D) Immune Globulin (Human)

Hyper**RHO**® Mini-Dose

DESCRIPTION

Rh_o(D) Immune Globulin (Human) — Hyper**RHO**® Mini-Dose is a clear or slightly opalescent and colorless or pale yellow sterile solution of human rho(D) immune globulin containing antibodies to Rh_o(D) for intramuscular administration; it contains no preservative. Hyper**RHO** Mini-Dose is prepared from pools of human plasma collected from healthy donors by a combination of cold ethanol fractionation, caprylate precipitation and filtration, caprylate incubation, anion exchange chromatography, nanofiltration and low pH incubation. Hyper**RHO** Mini-Dose is formulated as a 15% to 18% protein solution at a pH of 4.1 to 4.8 in 0.16 M to 0.26 M glycine. One dose of Hyper**RHO** Mini-Dose contains not less than one-sixth the quantity of Rh_o(D) antibody contained in one standard dose of Rh_o(D) Immune Globulin (Human), and it will suppress the immunizing potential of 2.5 mL of Rh_o(D) positive packed red blood cells or the equivalent of whole blood (5 mL). The quantity of Rh_o(D) antibody in Hyper**RHO** Mini-Dose is not less than 250 IU (50 mcg) per 1 mL.

When medicinal biological products are administered, the risk of infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogen.

In the manufacturing process of Hyper**RHO** Mini-Dose, there are several steps with the capacity for viral inactivation or removal.(1) The main steps of the manufacturing process that contribute to the virus clearance capacity are as follows:

- Caprylate precipitation/depth filtration
- Caprylate incubation
- Depth filtration
- Column chromatography
- Nanofiltration
- Low pH final container incubation

To provide additional assurance of the pathogen safety of the final product, the capacity of the Hyper**RHO** Mini-Dose manufacturing process to remove and/or inactivate viruses has

been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

The combination of all of the above-mentioned measures provides the final product with a high margin of safety from the potential risk of transmission of infectious viruses.

The caprylate/chromatography manufacturing process was also investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD) and Creutzfeldt-Jakob disease (CJD) agents.(1) These studies provide reasonable assurance that low levels of CJD/vCJD agent infectivity, if present in the starting material, would be removed by the caprylate/chromatography manufacturing process.

CLINICAL PHARMACOLOGY

Rh sensitization may occur in nonsensitized Rh_o(D) negative women following transplacental hemorrhage resulting from spontaneous or induced abortions.(2,3) The risk of sensitization is higher in women undergoing induced abortions than in those aborting spontaneously.(3-4)

Hyper**RHO** Mini-Dose is used to prevent the formation of anti-Rh_o(D) antibody in Rh_o(D) negative women who are exposed to the Rh_o(D) antigen at the time of spontaneous or induced abortion (up to 12 weeks' gestation).(4-6) Hyper**RHO** Mini-Dose suppresses the stimulation of active immunity by Rh_o(D) positive fetal erythrocytes that may enter the maternal circulation at the time of termination of the pregnancy.

The amount of anti-Rh_o(D) in Hyper**RHO** Mini-Dose has been shown to effectively prevent maternal isosensitization to the Rh_o(D) antigens following spontaneous or induced abortion occurring up to the 12th week of gestation.(7-9) After the 12th week of gestation, a standard dose of Hyper**RHO** Full Dose is indicated.

In a clinical study in 12 healthy human adults receiving another hyperimmune immune globulin product, Rabies Immune Globulin (Human), Hyper**RAB**®, prepared by the same manufacturing process, detectable passive antibody titers were observed in the serum of all subjects by 24 hours post injection and persisted through the 21 day study period.

INDICATIONS AND USAGE

Hyper**RHO** Mini-Dose is recommended to prevent the isoimmunization of Rh_o(D) negative women at the time of spontaneous or induced abortion of up to 12 weeks' gestation provided the following criteria are met:

1. The mother must be Rh_o(D) negative and must not already be sensitized to the Rh_o(D) antigen.
2. The father is not known to be Rh_o(D) negative.
3. Gestation is not more than 12 weeks at termination.

Note: Rh_o(D) Immune Globulin (Human) prophylaxis is not indicated if the fetus or father can be determined to be Rh negative. If the Rh status of the fetus is unknown, the fetus must be assumed to be Rh_o(D) positive, and Hyper**RHO** Mini-Dose should be administered to the mother.

FOR ABORTIONS OR MISCARRIAGES OCCURRING AFTER 12 WEEKS' GESTATION, A STANDARD DOSE OF Rh_o(D) IMMUNE GLOBULIN (HUMAN) IS INDICATED.

Hyper**RHO** Mini-Dose should be administered within 3 hours or as soon as possible after spontaneous passage or surgical removal of the products of conception. However, if Hyper**RHO** Mini-Dose is not given within this time period, consideration should still be given to its administration since clinical studies in male volunteers have demonstrated the effectiveness of Rh_o(D) Immune Globulin (Human) in preventing isoimmunization as long as 72 hours after infusion of Rh_o(D) positive red cells.(10)

CONTRAINDICATIONS

None known.

WARNINGS

HyperRHO Mini-Dose is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by including manufacturing steps that inactivate and/or remove viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Therapeutics LLC [1-800-520-2807].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

NEVER ADMINISTER HYPER**RHO** MINI-DOSE INTRAVENOUSLY. INJECT ONLY INTRAMUSCULARLY. ADMINISTER ONLY TO WOMEN POSTABORTION OR POSTMISCARRIAGE OF UP TO 12 WEEKS' GESTATION. NEVER ADMINISTER TO THE NEONATE.

Hyper**RHO** Mini-Dose should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immune globulin preparations.

The attending physician who wishes to administer Hyper**RHO** Mini-Dose to persons with isolated immunoglobulin A (IgA) deficiency must weigh the benefits of immunization against the potential risks of hypersensitivity reactions. Such persons have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders.

PRECAUTIONS

General

Although systemic reactions to immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactic symptoms.

Drug Interactions

Other antibodies in the in the Hyper**RHO** Mini-Dose preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live vaccines should not be given within 3 months after Hyper**RHO** Mini-Dose administration.

Pregnancy

Animal reproduction studies have not been conducted with Hyper**RHO** Mini-Dose. It is also not known whether Hyper**RHO** Mini-Dose can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

It should be again noted, however, that Hyper**RHO** Mini-Dose is **not** indicated for use during pregnancy and it should be administered only postabortion or postmiscarriage.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Reactions to Hyper**RHO** Mini-Dose are infrequent in Rh_o(D) negative individuals and consist primarily of slight soreness at the site of injection and slight temperature elevation. While sensitization to repeated injections of human globulin is extremely rare, it has occurred.

DOSAGE AND ADMINISTRATION

NEVER ADMINISTER HYPER**RHO** MINI-DOSE INTRAVENOUSLY. INJECT ONLY INTRAMUSCULARLY. ADMINISTER ONLY TO WOMEN POSTABORTION OR

POSTMISCARRIAGE OF UP TO 12 WEEKS' GESTATION. NEVER ADMINISTER TO THE NEONATE.

One syringe of Hyper**RHO** Mini-Dose provides sufficient antibody to prevent Rh sensitization to 2.5 mL Rh_o(D) positive packed red cells or the equivalent (5 mL) of whole blood. This dose is sufficient to provide protection against maternal Rh sensitization for women undergoing spontaneous or induced abortion of up to 12 weeks' gestation.

Rh_o(D) Immune Globulin (Human) — Hyper**RHO**® Mini-Dose (250 IU; 50 mcg) should be administered within 3 hours or as soon as possible following spontaneous or induced abortion. If prompt administration is not possible, Hyper**RHO** Mini-Dose should be given within 72 hours following termination of the pregnancy.

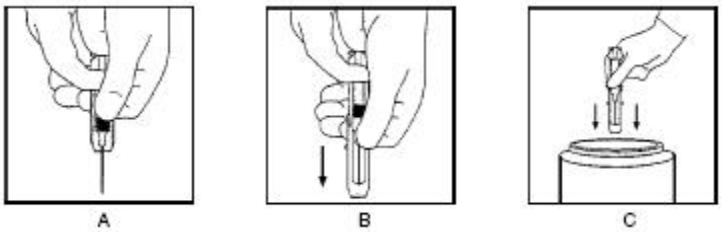
Hyper**RHO** Mini-Dose is administered **intramuscularly**, preferably in the deltoid muscle of the upper arm or lateral thigh muscle. The gluteal region should not be used as an injection site because of the risk of injury to the sciatic nerve.(11)

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Hyper**RHO** Mini-Dose is supplied with a syringe and an attached needle guard for your protection and convenience. Please follow instructions below for proper use of syringe and needle guard.

Directions for Syringe Usage

1. Remove the prefilled syringe from the package. Lift syringe by barrel, **not** by plunger.
2. Twist the plunger rod clockwise until the threads are seated. Do not use if the syringe is prematurely engaged.
3. With the rubber needle shield secured on the syringe tip, push the plunger rod forward a few millimeters to break any friction seal between the rubber stopper and the glass syringe barrel.
4. Remove the needle shield and expel air bubbles. [Do not remove the rubber needle shield to prepare the product for administration until immediately prior to the anticipated injection time.]
5. Proceed with hypodermic needle puncture.
6. Aspirate prior to injection to confirm that the needle is not in a vein or artery.
7. Inject the medication.
8. Keeping your hands behind the needle, grasp the guard with free hand and slide forward toward needle until it is completely covered and guard clicks into place. If audible click is not heard, guard may not be completely activated. (See Diagrams A and B)
9. Place entire prefilled glass syringe with guard activated into an approved sharps container for proper disposal. (See Diagram C)



A B C

A number of factors could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

HOW SUPPLIED

Hyper**RHO** Mini-Dose is available in a single-dose syringe with attached needle. The Hyper**RHO** Mini-Dose package contains 10 single-dose syringes. Hyper**RHO** Mini-Dose contains no preservative and is not made with natural rubber latex.

NDC Number	Size
13533-661-06	Syringe (10 pack)

STORAGE

Store at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use after expiration date. Discard unused portion.

CAUTION

℞ only

U.S. federal law prohibits dispensing without prescription.

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11. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). General recommendations on immunization. *MMWR* 2002;51(RR02):1-36.

(Rev. M/202X)

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The Rh Factor and Your Pregnancy

Information About Pregnancy Protection

The Rh Factor and When It Is Important

The Rh factor is one of many blood group antigens found on the surface of red blood cells. If you have this antigen you are considered Rh positive. If you don't, then you are considered Rh negative. Everyone is either Rh positive or Rh negative. One type is neither better nor worse than the other, only different.

Your Rh factor is important if you are an Rh negative woman and you become pregnant, or if you receive a blood transfusion.

How the Rh Factor Can Affect Your Future

If you have Rh negative blood, there are two situations that can affect you:

1. If the father of your baby is Rh positive, the baby will probably be Rh positive too. An Rh negative woman carrying an Rh positive baby may have an immune reaction if some of the baby's Rh positive blood cells enter her bloodstream.

   This immune reaction, called isoimmunization, means your body's defense system recognizes Rh positive blood as foreign from your own and produces "antibodies" to destroy the invading Rh positive blood cells.

   The passage of blood from the baby to the mother's bloodstream happens most often at delivery, but can also occur during miscarriage, the termination of pregnancy, amniocentesis (test performed to determine fetal health), or due to an injury or trauma. It is important to note that a small number of women develop antibodies to Rh positive blood cells during pregnancy for no apparent reason.

   Antibodies to Rh positive blood may not be a problem in first pregnancies; however, the antibodies stay in your bloodstream, ready to attack invading Rh positive blood cells, for many years to come. This can lead to problems in future pregnancies by causing miscarriage or a disease known as hemolytic disease of the newborn.

   Babies born to Rh positive mothers, regardless of the father's blood type, will usually be free of the dangers of hemolytic disease.

2. Someday it may become necessary for you to receive a blood transfusion. If Rh positive antibodies already reside in your bloodstream due to isoimmunization and the blood you receive is Rh positive due to error or lifesaving reasons, your Rh positive antibodies will become mobilized and destroy the donor Rh positive cells. As a result, the transfusion could be unsuccessful and possibly harmful to you.

Hemolytic Disease of the Newborn: A Threat to Your Baby

When an Rh negative woman has Rh positive antibodies in her blood and the baby she is carrying is Rh positive, the antibodies could possibly enter the baby's bloodstream, attack the baby's red blood cells and cause hemolytic disease of the newborn. At birth, the infant suffering from hemolytic disease may be jaundiced and anemic or suffer permanent damage of the brain and central nervous system which may result in mental retardation, hearing loss, or cerebral palsy. Extensive medical care can be required, including an exchange transfusion, in which all of the baby's blood is replaced. This usually stops the destruction of the baby's red blood cells and gives the infant a chance to survive.

The risk of hemolytic disease of the newborn is slight with the first baby, but increases with each successive pregnancy.

Preventing Hemolytic Disease

Hyper**RHO**®, Rh_o(D) Immune Globulin (Human), can prevent hemolytic disease of the newborn, provided Rh positive antibodies do not already reside in your bloodstream.

Hyper**RHO** is a specially prepared gamma globulin with a high level of preformed antibodies against Rh positive blood cells. The injection of Hyper**RHO** destroys any Rh positive blood cells that may have entered the mother's bloodstream and prevents the mother's immune system from producing Rh positive antibodies; thus protecting the baby from developing hemolytic disease.

HyperRHO Full Dose — When Prescribed

Pregnancy and Other Obstetric Conditions Pertaining to Rh Negative Women

Hyper**RHO** Full Dose (1500 IU; 300 mcg) is administered during pregnancy if you fall into a high-risk category. For example, you are at risk of producing Rh positive antibodies if you have an amniocentesis procedure performed, or if you have a miscarriage or other termination of pregnancy at or beyond 13 weeks' gestation.

Laboratory findings have shown that some Rh negative women develop Rh positive antibodies during the last weeks of pregnancy even without an antibody-stimulating event. As a preventive measure, your physician will probably recommend the first injection of Hyper**RHO** Full Dose at the 28th week of pregnancy.

In both of the above situations, if the blood type of the father or baby can be determined to be Rh negative, an injection of Hyper**RHO** is not required.

Another injection of Hyper**RHO** Full Dose is administered within 72 hours of delivery of an Rh positive baby.

Blood Transfusion

Hyper**RHO** Full Dose (1500 IU; 300 mcg) may be used to prevent isoimmunization in Rh negative individuals who have been transfused with Rh positive red blood cells or blood components containing red blood cells.

HyperRHO Mini-Dose — When Prescribed

A single dose of Hyper**RHO** Mini-Dose (250 IU; 50 mcg) may be prescribed for an Rh negative woman instead of Hyper**RHO** Full Dose (1500 IU; 300 mcg) in the event of miscarriage or other termination of pregnancy occurring **prior** to 13 weeks' gestation. Hyper**RHO** Mini-Dose is not required if the blood type of the father or fetus can be determined to be Rh negative.

Will You Need HyperRHO Again?

Hyper**RHO** provides protection only if you have not already produced Rh positive antibodies. Women who have developed antibodies through previous pregnancy, miscarriage, other termination of pregnancy, or blood transfusion cannot be protected by Hyper**RHO**. This is why with each pregnancy it is important to have Hyper**RHO** injections within the prescribed time period.

Reactions to HyperRHO

You may feel a temporary soreness at the site of the injection. You may also have a slight and temporary change in body temperature. In very rare instances, an allergic type of reaction can occur, for which your physician will take appropriate measures.

Delivering a Sound, Healthy Baby

Your physician can answer any questions you may have about receiving a Hyper**RHO** injection to prevent hemolytic disease of the newborn. If you know that you are Rh negative and you are pregnant, you should discuss your situation with your physician. Today, with Hyper**RHO**, hemolytic disease of the newborn can be reduced to its lowest possible rate of incidence.

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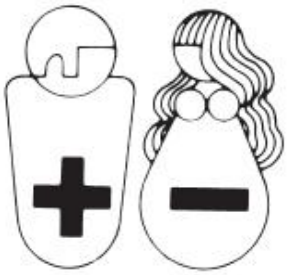
Development of Hemolytic Disease

1

Rh positive (+) father.

Rh negative (–) mother.

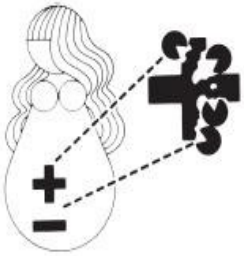


2

Pregnancy: Rh– mother is carrying Rh+ baby.

3

The passage of Rh+ blood from the baby to the mother's bloodstream happens most often at delivery, but can also occur during miscarriage, other termination of pregnancy, amniocentesis, or due to injury or trauma.



4

Rh+ antibodies stay in your bloodstream, ready to attack invading Rh+ blood cells, for many years to come.

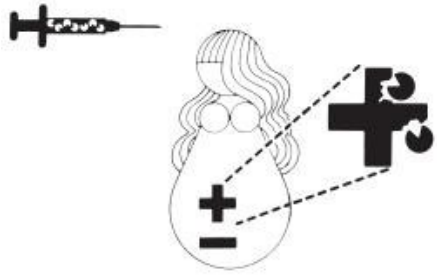
5

Next pregnancy, mother’s Rh+ antibodies enter baby’s Rh+ bloodstream, attacking baby’s blood cells and causing hemolytic disease of the newborn.

How HyperRHO Immune Globulin Can Prevent Hemolytic Disease

1

You will probably be given two injections of Hyper**RHO** Full Dose, one at the 28th week of your pregnancy and another within 72 hours of delivery, miscarriage or other termination of pregnancy. A single injection of Hyper**RHO** Mini-Dose may be prescribed instead of Hyper**RHO** Full Dose in the event of miscarriage or other termination of pregnancy occurring prior to 13 weeks' gestation.



2

Hyper**RHO** immunization prevents formation of mother's own Rh+ antibodies. Mother’s bloodstream remains free of Rh+ antibodies.

3

Next pregnancy, baby develops normally. Hyper**RHO** should be administered following delivery, miscarriage, or other termination of pregnancy to continue protection if baby is Rh+.